

REMARKS

I. Status of the Claims

Claims 1-15 were originally filed. As the result of a restriction requirement, claims 10 and 11 have been withdrawn from consideration and are now canceled. Claims 1-9 and 12-15, to the extent they read on SEQ ID NO:8, are under examination. Upon entry of the present amendment, claims 1 and 12 are amended to recite a greater than 90% sequence identity, support for which can be found in the specification, *e.g.*, on page 5, lines 24-28. Recitation of specific binding to polyclonal antibodies is replaced with recitation of forming a functional ion channel, which finds support in the specification, *e.g.*, on page 9, lines 22-23. Claim 12 is further amended to correct a typographic error. No new matter is introduced.

II. Amendment to the Specification

The specification is amended to delete all reference to browser-executable codes embedded in the text. The amendment further corrects some typographic errors. No new matter is introduced.

III. Objection to the Oath/Declaration

The Examiner alleged that the oath/declaration filed in the present application is defective because the inventors' citizenship and residence are not provided. Applicants respectfully call the Examiner's attention to the Application Data Sheet filed with the present application on December 21, 2001, where the residential address and citizenship of the inventors are clearly provided. The withdrawal of this objection is respectfully requested.

IV. Claim Rejections

A. 35 U.S.C. §112, First Paragraph

Enablement Rejection

Claims 1-9 and 12-15 were rejected under 35 U.S.C. §112, first paragraph, for alleged inadequate enablement. Applicants respectfully traverse the rejection.

A claimed invention is enabled when the disclosure allows one of ordinary skill in the art to make and use the invention without undue experimentation. MPEP §2164.01. The test for enablement as set forth in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), requires the consideration of multiple factors: the breadth of the claims; the nature of the invention; the state of the prior art; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In the present case, the claims are directed to a method for identifying compounds that modulate taste signaling in taste cells. The method comprises the following steps:

(i) contacting the compound with a eukaryotic host cell or cell membrane which expresses a taste cell-specific ion channel subunit: (a) having greater than about 90% amino acid sequence identity to a polypeptide having a sequence selected from the group that consists of SEQ ID NO: 2, SEQ ID NO: 5, and SEQ ID NO: 8; and (b) forming a functional ion channel; and

(ii) determining a functional effect of the compound upon a transmembrane ion flux of a predetermined ion, thereby identifying a compound that modulates taste signaling in taste cells.

The pending claims are also directed to a method for modulating taste signaling in taste cells in an individual, by administering an effective amount of a composition capable of modulating taste signaling by an ion channel having the features of (a) and (b) as described above. The specification contains ample guidance to practice the invention, such as methods for obtaining the polynucleotide coding sequence of a taste cell-specific ion channel subunit (*see, e.g.*, page 33 line 30 to page 36 line 4), expression of the ion channel subunit (*see, e.g.*, page 36 line 6 to page 38 line 20), purification of the ion channel subunit (*see, e.g.*, page 38 line 23 to page 41 line 18), assays for measuring the activity of a taste cell-specific ion channel subunit (*see, e.g.*, page 23 line 1 to page 28 line 19), and formulation and administration of a modulator of taste signaling (*see, e.g.*, page 49 line 27 to page 51 line 6).

As described in the specification, abundant knowledge relating to the TRP family ion channels is available. This information allows the determination of crucial amino acids for functionality of the ion channels. Thus, a skilled artisan may rely on such knowledge to create variants of ion channel proteins, *e.g.*, those with greater than 90% amino acid sequence identity to an exemplary sequence (such as SEQ ID NO:2, 5, or 8). The level of technical sophistication is high in the art, which allows taste cell-specific ion channel subunit variants having an amino acid sequence other than the exemplary sequences (*e.g.*, SEQ ID NO:2, 5, or 8) to be readily tested according to the methods commonly used by those skilled in the art or the methods taught by the specification (such as nucleic acid or amino acid sequence comparison and functional assays for ion channel subunits specific for taste cells), so that inoperable embodiments can be readily eliminated. The available knowledge and techniques in the art combined with the teaching of the specification also allow one of skill in the art to readily examine the functional effect of a candidate compound on a taste cell-specific ion channel subunit and identify a modulator of taste signaling. MPEP §2164.01 states, complex experimentation is not necessarily undue, if the art typically engages in such experimentation. In the present case, although some experimentation may be involved to practice the claimed invention using taste cell-specific ion channel subunits other than those specifically described in the application, such experimentation utilizes well-established techniques and is the type routinely conducted in the art. Thus, the experimentation does not constitute undue experimentation.

In raising the enablement rejection, the Examiner expressed concerns over several specific issues. First, the Examiner asserted that specific proteins associated with the taste cell-specific ion channel subunit in taste signaling need to be identified for the practice of the claimed method, particularly in claim 5, which relates to an isolated cell membrane comprising the ion channel subunit. Applicants do not agree. Given the fact that various aspects of taste signaling can be used in measuring a functional effect a candidate compound might have on a taste cell-specific ion channel subunit, associated proteins need not be identified or supplied for the screening method, because at least the changes in parameters upstream from the associated

proteins can still be used. For example, changed ion flux mediated by the ion channel subunit can be just such an upstream event.

Second, the Examiner contended that the specification does not teach which amino acid substitutions can be made to the exemplary sequences such as SEQ ID NO:8. Applicants respectfully argue that, by disclosing several related taste cell-specific ion channel subunit sequences, such as SEQ ID NO:2 and SEQ ID NO:5, the specification in fact allows one of skill in the art to compare these amino acid sequences and obtain valuable information as to which amino acid residues are likely critical and therefore should not be modified (*i.e.*, those residues that are highly conserved among the three sequences), and which amino acid residues are likely to tolerate substitution without loss of function (*i.e.*, those that are not conserved among the sequences). This specific disclosure is further in the context of the general knowledge of TRP family of ion channels available to those of skill in the art, such as the information provided by the references cited in the specification (*e.g.*, on page 53, lines 8-24). In addition, the functional aspect of any variants can be readily tested according to the specification (*e.g.*, page 23 line 1 to page 28 line 19) such that inoperable variants can be quickly identified and excluded. Thus, Applicants submit that the specification does provide sufficient guidance for an ordinarily skilled artisan to obtain taste cell-specific ion channel subunit variants for the practice of the claimed invention.

Taken together, analysis of the *Wands* factors indicates proper enablement of the claimed invention, whereas the Examiner's specific concerns are also addressed. Applicants thus respectfully request the withdrawal of the enablement rejection.

Written Description Rejection

Claims 1-9 and 12-15 were also rejected under 35 U.S.C. §112, first paragraph, for alleged inadequate written description. Applicants respectfully traverse the rejection.

Possession of claimed invention may be shown by a variety of descriptive means, including words, structure, figures, diagrams, and formulas. MPEP §2163 I. Case law provides more specific guidance in setting the standard for written description.

As discussed above, the amended claims are directed to a method for identifying compounds that modulate taste signaling in taste cells, as well as a method for modulating taste signaling in taste cells in an individual. Both of the claimed methods rely on the use of a taste cell-specific ion channel subunit having the following features: (a) having greater than about 70% amino acid sequence identity to a polypeptide having a sequence selected from the group that consists of SEQ ID NO: 2, SEQ ID NO: 5, and SEQ ID NO: 8; and (b) forming a functional ion channel. Applicants contend that the amended claims fully comply with the requirements for written description of a chemical genus as set forth in *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). As described by the Federal Circuit in *Lilly*, “[a] description of a genus of cDNAs may be achieved by means of . . . a recitation of structural features common to the members of the genus” *Lilly*, 43 USPQ2d at 1406. Furthermore, the court in *Fiers v. Revel* stated that an adequate written description “requires a precise definition, such as by structure, formula, chemical name, or physical properties.” *Fiers*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993).

The recited amino acid sequence identity to a reference sequence, such as SEQ ID NO:2, 5, or 8, is a physical/structural property of the taste cell-specific ion channel used in the claimed screening method of this application, because such sequence identity relies upon the amino acid sequence of the ion channel polypeptide. Thus, pending claims set forth commonly shared structural features of the claimed nucleic acids.

On the other hand, proper description of functional features of a claimed invention can play an important role in satisfying the written description requirement. The Federal Circuit recently stated that “*Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.” *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 65 USPQ2d 1385, 1398 (Fed. Cir. 2003). To this end, the functional features of the taste cell-specific ion channel subunit used in the claimed screening method are also provided: the subunit must be able to form a functional ion channel. As stated above, various methods are well

known in the art for verifying the function of an ion channel. The specification also teaches such methods, particularly those for testing a taste cell-specific ion channel (*see, e.g.*, page 23 line 1 to page 28 line 19).

The Examiner apparently took the position that, besides SEQ ID NO:2, 5, or 8, the instant application does not adequately describe a genus of taste cell-specific ion channel polypeptides that can be used in the claimed screening method, because no additional sequences were disclosed. Applicants cannot agree. As already discussed in the previous sections, at the time this application was filed, other TRP family ion channels were known in the art. This knowledge, combined with the level of recombinant technology, would allow an artisan to reasonably recognize that when the present inventors took possession of these exemplary sequences (SEQ ID NOs:2, 5, and 8), the inventors were in effect also in possession of a genus of polypeptides, which could be readily produced and verified functionally based on the well established techniques and general knowledge of the family of ion channels.

The fact pattern of the present case is completely different from that of *Fiddes v. Baird*, which the Examiner cited to support the written description rejection. In *Fiddes*, a broad claim was drawn to mammalian FGF based on the specification disclosing a bovine FGF amino acid sequence and a *deduced* nucleotide sequence, but not any naturally occurring FGF nucleotide sequence. As it later turned out, the deduced nucleotide sequence disclosed in the specification is significantly different from the naturally occurring FGF nucleotide sequence, largely due to codon degeneracy. In essence, the patent applicants in *Fiddes* sought to patent a large genus of polypeptide and polynucleotides when they did not have in their possession any correct polynucleotide sequence. The Board's finding of inadequate written description was based on the notion that the claim of a genus of polynucleotides cannot be adequately supported when only an *inaccurate* polynucleotide sequence was disclosed. The Board in *Fiddes* did not take the position that the claim of a genus cannot be adequately supported by the disclosure of an *accurate* polynucleotide sequence. Nor could the Board, under *Lilly*, properly require the claim of a genus to be supported by the patent applicant's possession of every embodiment of the genus.

In contrast to *Fiddes*, the present inventors have in their possession both the amino acid sequence of several taste cell-specific ion channel polypeptide (SEQ ID NOs:2, 5, and 8) and the naturally occurring nucleotide sequence encoding the polypeptides in full length (SEQ ID NOs: 1, 4, and 7). In addition, the claims in the present application are not drawn to a broad genus of molecules without specific structural definition (such as a simply recitation of mammalian taste cell-specific ion channel). As discussed above, the structural features commonly shared by the genus have been described in detail, which "clearly allow persons of ordinary skill in the art to recognize that [the applicant] invented what is claimed." *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991).

Taken together, the disclosure by the present application provides the commonly shared structural/physical features of the genus of taste cell-specific ion channel polypeptides used in the claimed screening method, fully satisfying the written description requirement under *Lilly* and *Fiers*. On the other hand, there exists crucial factual distinction between the present case and *Fiddes v. Baird*, which would make it improper to apply *Fiddes* mechanically. As such, Applicants respectfully request that the Examiner withdraw the written description rejection.

B. 35 U.S.C. §102

Claims 1-9 and 12-15 were rejected under 35 U.S.C. §102(e) for alleged anticipation by U.S. Patent Application Publication 2002/0037515, which was filed April 13, 2001, and claims priority to USSN 60/197,491, filed April 17, 2000. Applicants respectfully traverse the rejection in light of the Rule 131 declaration filed herewith.

In the Rule 131 declaration accompanying this communication, the two named inventors on this application, Drs. Zuker and Zhang, state that they completed the claimed invention in the United States prior to April 17, 2000, the filing date of USSN 60/197,491. Offered as evidence are Exhibits I-V, which are described as follows in paragraph 4 of the declaration:

Exhibit I is pages of a printout of a sequence file containing the polynucleotide sequence of 930 clones obtained from a subtracted cDNA library prepared from rat circumvallate

cells, following the experimental procedure described in Example I of the application. The pages of Exhibit I indicate the date of last modification to contiguous sequence ("contig") No. 068-3 157 501 and the polynucleotide sequence of clone 501, one of the three clones that make up this contig.

Exhibit II is pages of laboratory notebook indicating that a Blast search was performed for known polynucleotide sequences matching each one of the 930 clones, including clone 501.

Exhibit III is the results of sequence alignment between the mouse Trpm5 (also known as Mtr1 and Ltrpc5) and clone 501, which indicate a high degree of homology.

Exhibit IV is the polynucleotide sequences of the mouse Trpm5 (GenBank No. NM_020277, derived from GenBank No. AJ271092, see page 2 of printout for NM_020277) and human Mtr1 (GenBank No. AF177473). The materials of exhibit indicate that these sequences were publicly accessible by January 14, 2000 (see page 1 of printout for AJ271092) and August 13, 1999 (see page 1 of printout for AF177473), respectively. Exhibit IV further includes results of a sequence alignment between the amino acid sequences encoded by mouse Trpm5 gene and human Mtr1 gene.

Exhibit V shows the results of an *in situ* hybridization experiment indicating the taste cell-specific expression of the gene from which clone 501 is derived, using a nucleic acid probe specific for clone 501, which was also referred to as 501-PCR46.

In paragraph 5 of the declaration, the inventors further explain that the conception of the present invention as well as its reduction to practice are evidenced by the Exhibits. For instance, it is explained that the first page of Exhibit I shows that contig No. 068-3 157 501 consists of three clones: 3, 157, and 501, the longest of which is clone 501. The second page shows the polynucleotide sequence of clone 501. The third page establishes the time of last modification made to contig No. 068-3 157 501 and therefore establishes the time when the sequence of clone 501 was determined. Upon determination of the polynucleotide sequence of

clone 501, a Blast search was conducted to identify known polynucleotide sequence(s) with high level of sequence homology with clone 501. This is evidenced by Exhibit II.

In paragraph 6 of the declaration, the inventors provide explanations of Exhibit III, which shows the identification of the mouse Trpm5 gene through this sequence homology-based search. According to the inventors, Exhibit III demonstrates that the mouse Trpm5 and clone 501 are highly homologous. Therefore, one of skill in the art would consider the rat gene from which clone 501 is derived to be the ortholog of mouse Trpm5. Although the particular sequence alignment presented in Exhibit III was performed at the present time, the inventors attest that the same result would have been (and was indeed) obtained at the time the initial Blast search was performed. This is because, as evidenced by Exhibit IV, the polynucleotide sequence of mouse Trpm5 was publicly accessible well before April 17, 2000. Moreover, the inventors point out that human Mtr1 and mouse Trpm5 have a greater than 84% identity in amino acid sequence, as shown by Exhibit IV. Based on this high level of sequence homology, the inventors attest that one of skill in the art would recognize human Mtr1 as the ortholog of mouse Trpm5.

In addition, the inventors explain that Exhibit IV also demonstrates the public availability of polynucleotide sequence of human Mtr1 gene well before April 17, 2000. Thus, a Blast search based on the sequence of clone 501 by the present inventors at the time indicated by Exhibit II necessarily led to the identification of both the human and mouse versions of the Mtr1 gene. Subsequently, *in situ* hybridization was performed to confirm the taste cell-specific expression of the rat version of this gene, shown in Exhibit V.

The Rule 131 declaration therefore establishes that the present inventors had identified the human, mouse, and rat Mtr1 genes as taste cell specific ion channels prior to April 17, 2000. U.S. Patent Application Publication 2002/0037515 is therefore not available as a prior art reference under 35 U.S.C. §102(e). The withdrawal of the anticipation rejection is hence respectfully requested.

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Amtd. dated April 28, 2005
Reply to Office Action of November 30, 2004

PATENT

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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